Dramatic Impact of ppb Levels of Palladium on the "Copper-Catalyzed" Sonogashira Coupling

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The palladium-catalyzed Sonogashira reaction is the most powerful synthetic methodology for the introduction of a triple bond into aromatic systems.[1] Since its discovery,[2] several developments have been achieved to perform the reaction more efficiently by using either homogeneous[3] or heterogeneous[4] palladium catalysts. This coupling required a palladium–copper catalyst mixture, but one of the early research directions focused on the development of a copper-free method[5] to suppress the copper-assisted Glaser-type homocoupling of the terminal acetylenes,[6] which often accompanies the desired Sonogashira reaction. By applying these conditions, in principle, the cheaper metal can be left out of the reaction. If one considers economical aspects, the omission of the expensive noble metal palladium, would surely be preferable to the exclusion of copper.

Keeping this idea in mind, several attempts have already been made to achieve the Sonogashira coupling in the absence of palladium, either in the presence of copper or other transition metals, or under completely transition-metal-free conditions. Although, in the latter case the reactions work well with microwave irradiation, even with aryl bromides as demonstrated by Leadbeater[7] and Van der Eycken,[8] it is possible that palladium contaminants might be responsible for the successful coupling. The effect of palladium impurities was demonstrated later by Leadbeater in the case of the Suzuki coupling of aryl halides.[9] Although iron[10] and gold[11] seemed to be suitable alternatives to palladium in the Sonogashira coupling, the significance of gold was found to be unlikely, as recently demonstrated by Espinet, Echavarren, and co-workers.[12] Moreover, the catalytic inactivity of iron has also been proved in the Suzuki reaction.[13]

The copper-catalyzed Sonogashira coupling has already been developed by several research groups.[14] Venkataraman designed and applied copper catalysts containing phosphanes and phenanthroline ligands for the coupling of terminal acetylenes with aryl iodides.[14h] The conditions developed by Taillefer and co-workers based on the application of 1,3-dicarbonyl ligands, allows for the Sonogashira coupling of electron deficient aryl iodides at 90°C.[14i] Although these palladium-free conditions work well for the Sonogashira reaction, the possible role of palladium contaminants has not been considered in these copper-catalyzed couplings. Inspired by findings of Bolm and others on the dramatic effect of ppm levels of copper catalyst in carbon–heteroatom bond-forming reactions,[15] and Plenio's note in connection with the palladium-free Sonogashira conditions,[16] we intended to examine the sensitivity of the copper-catalyzed Sonogashira-type coupling of aryl iodides to palladium impurities.

The complete separation of palladium- and copper-catalyzed processes in the Sonogashira reaction is quite complicated. First, it is challenging to set up reactions containing only one of the metals (copper or palladium), especially when the impurity level is held to a minimum (ppb level).[5h] Secondly, the supposed mechanism of the classic palladium-catalyzed transformation includes a copper-assisted transmetalation step, which requires a copper co-catalyst (Scheme 1). As a consequence, in a catalytic cycle based on a copper catalyst (Scheme 1, cycle A) the so-formed copper acetylide species (**3**) may react with the aryl palladium halide (**8**) and enter into the palladium cycle (Scheme 1, cycle B), even if the amount of this palladium adduct is negligible at the first glance (ppb level). Considering the dual existence of two possible operating cycles, we cannot be certain that the coupled product (**10**) forms through the copper cycle (cycle A) or the palladium cycle (cycle B).

During our preliminary studies we have found that not only the purity of the copper source is important, but the purity of the base, the acetylene, and the equipment should

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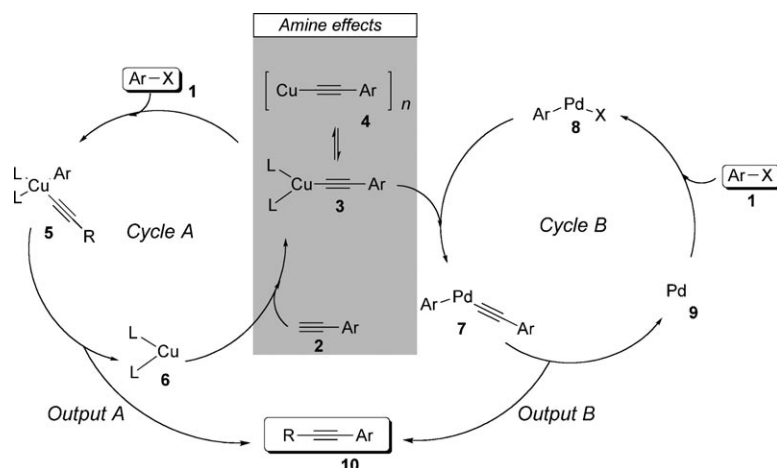
Scheme 1. Proposed mechanism of the copper- and palladium-catalyzed synergistic coupling of acetylenes and aryl halides.

also be considered.[17] With the use of 2.5 mol % Cu-(PPh₃)₂NO₃ prepared from Cu(NO₃)₂ (with 99.999 % purity), the coupling of phenylacetylene and iodobenzene afforded the desired diphenylacetylene with only 1 % conversion after 24 h in toluene at 110 °C. Reactions carried out with 2.5 mol % and 10 mol % of Venkataraman's Cu-PhenPPh₃NO₃ complex showed 14 % and 25 % conversions, respectively, after 24 h, which is significantly lower than the value described earlier.[14f,h,18]

Systematic studies on the effect of palladium have revealed the high sensitivity of the coupling to palladium contaminants, Figure 1 shows the dependence of the conversion on [PdCl₂(PPh₃)₂] loading in the range of 0–10 ppm. Even the presence of 100 ppb of palladium complex caused significant rate acceleration and the use of 10 ppm of palladium
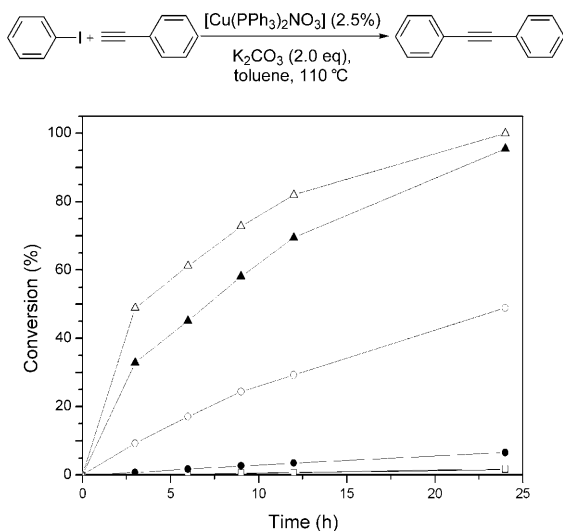

Figure 1. Effect of palladium content on the coupling of iodobenzene and phenylacetylene. Reaction conditions: [Cu(PPh₃)₂NO₃] (0.025 mmol, 2.5 mol %), iodobenzene (1.0 mmol), phenylacetylene (1.0 mmol), K₂CO₃ (2.0 mmol), 110 °C, argon. Conversions were determined by GC. ■ = 0, □ = 1, ● = 10, ○ = 100, ▲ = 1000, △ = 10000 ppb Pd.

led to complete coupling in 24 h in the case of both copper catalysts.[19]

Amines are more frequently used than inorganic bases for the traditional palladium-catalyzed Sonogashira coupling. Furthermore, they have multiple roles both in the single metal-catalyzed and palladium–copper systems. These organic bases enhance the deprotonation of the acetylene and are able to coordinate to both the copper and the palladium. By coordination to the copper, the formation of monomeric copper acetylide (**3**) is favored over the unreactive polynuclear species (**4**) (Scheme 1, amine effects).[20,21]

In the course of examining the amine effect, in the presence of K₂CO₃ (2.0 equiv) and 30 mol % of *n*-hexylamine, *N,N*-DMEDA, *N,N′*-DMEDA, TMEDA, or phenanthroline (DMEDA = dimethylethylenediamine, TMEDA = tetramethylethylenediamine) we observed 10, 17, 40, 7, and 10 % conversions, respectively, after 24 h in the [Cu(PPh₃)₂NO₃] catalyzed coupling of iodobenzene with phenylacetylene at 110 °C. Amongst these bases *N,N′*-DMEDA proved to be the most efficient and other bases showed moderate activity. Additionally, application of 1,3-bis(diphenylphosphanyl)propane (dppp) as a good coordinating, but non-basic ligand completely shut down the reaction.[22] These results support our assumption regarding the importance of both basic character and coordinating ability of the amine.[21,23]

The examination of the effect of palladium on the [Cu(PPh₃)₂NO₃]-catalyzed reaction in the presence of amine showed the system is even more sensitive to palladium. Addition of 30 mol % *N,N′*-DMEDA ensures almost complete conversion even with 100 ppb palladium in 24 h. Bidentate amines *N,N*-DMEDA and *N,N′*-DMEDA are still more efficient than hexylamine, but the differences in conversions are significantly smaller than those found in the absence of palladium.[22,24]

Comparison of the palladium content–conversion curves (Figure 2) shows that even 10 ppb of added palladium significantly accelerates the transformation in the presence of hexylamine.[25]

Examination of different types of palladium sources showed that the type of the palladium source had no significant influence on the reaction.[26] Application of 100 ppb [PdCl₂(PPh₃)₂], Pd(OAc)₂, [Pd₂dba₃] (dba = dibenzylidene-acetone), and [Pd(PPh₃)₄] catalysts in the presence of hexylamine gave 46–55 % conversion after 6 h and 83–90 % in 24 h.

Only the [PdCl₂(dppp)], complex produced lower reactivity compared with other palladium sources (11 and 36 % conversions after 6 and 24 h, respectively). The inhibition effect
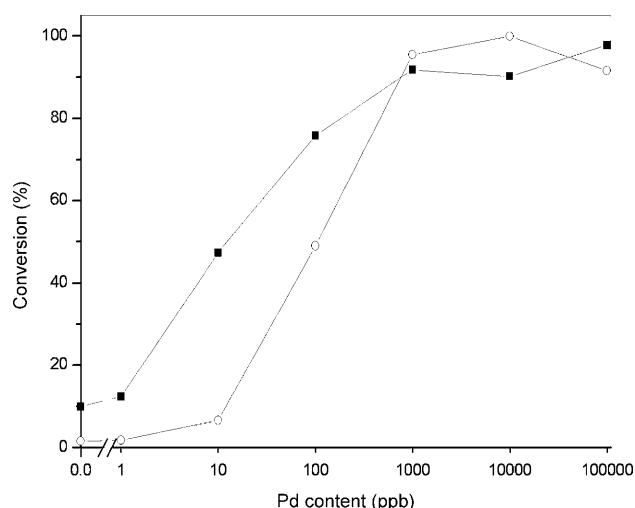
Figure 2. Effect of palladium content on the coupling of iodobenzene and phenylacetylene in the absence (○) and in the presence of 30 mol% hexylamine (■). Reaction conditions: [Cu(PPh$_3$)$_2$NO$_3$] (0.025 mmol, 2.5 mol%), iodobenzene (1.0 mmol), phenylacetylene (1.0 mmol), K$_2$CO$_3$ (2.0 mmol), 110°C, argon. Conversions were determined after 24 h reaction time by GC.

of the bidentate phosphane ligand on the palladium catalysis is congruent with our earlier observation regarding the deleterious effect of dppp on the [Cu(PPh$_3$)$_2$NO$_3$]-catalyzed reaction. We suppose that the addition of chelating phosphanes diminished the activity of the palladium catalysts in the coupling.

Relying on literature data and inductively coupled plasma mass spectrometry (ICP-MS) analysis regarding the ppb levels of palladium contents of some reactants[27] used for the reaction, coupled with the observed sensitivity of the reaction to traces of palladium, we questioned the relevance of copper catalysis under the applied conditions. To exclude the copper cycle, we next examined the copper loading dependence on the reaction, both in the presence and in the absence of added palladium. The copper loading–conversion curves showed saturation profiles in the range of 0–2.5 mol% independent to the amount of amine (15, 30, 60 mol% hexylamine) used for the reactions (Figure 3, top). Although, these observations correlate with Bolm's findings[21] and can be explained with the polymeric resting state of the formed copper acetylide, further increase of the copper loading (up to 40%) accelerated the reaction (Figure 3, bottom). The observed copper loading dependence suggests that the copper may act both as a catalyst or just a co-catalyst and palladium supplier for a traditional palladium-catalyzed Sonogashira coupling.[28]

Contrary to the observed experimental results rate, acceleration should not be observed when the copper loading increases, if one considered both the relevance of polymer formation from the copper and acetylene, and pure copper catalysis. Decreasing the amine/copper ratio (by increasing the copper loading, while maintaining the amount of amine) shifts the polymer–monomer equilibrium to the formation of catalytically inactive polynuclear acetylide species. At a
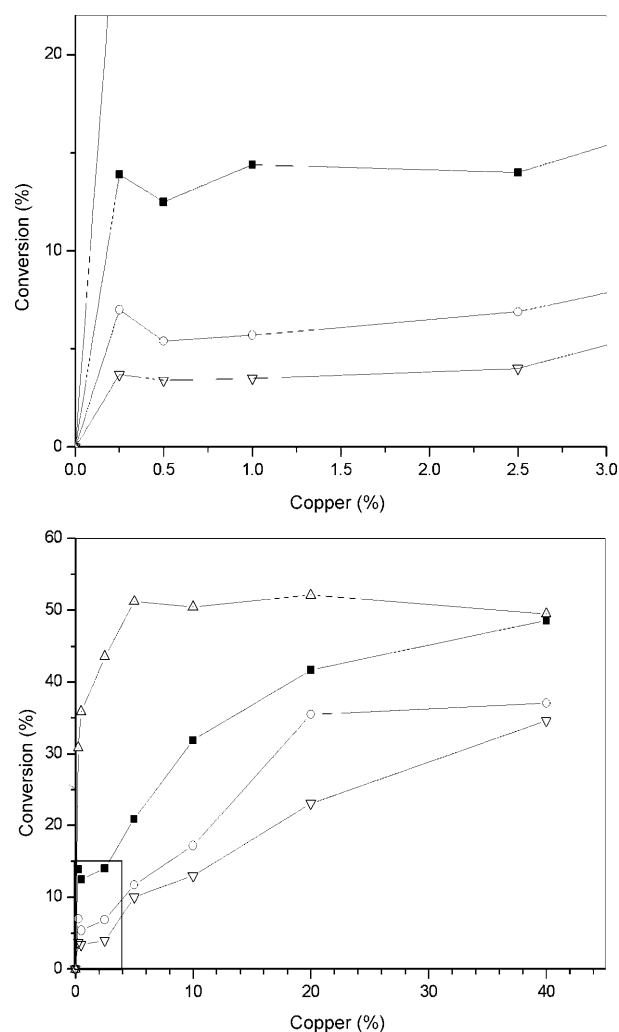

Figure 3. Effect of copper loading on the coupling of iodobenzene and phenylacetylene in the absence and in the presence of palladium. Reaction conditions: [Cu(PPh$_3$)$_2$NO$_3$] (0.025 mmol, 2.5 mol%), iodobenzene (1.0 mmol), phenylacetylene (1.0 mmol), hexylamine (0, 0.15, 0.3, or 0.6 mmol), K$_2$CO$_3$ (2.0 mmol), 110°C, argon. Conversions after 24 h were determined by GC. ■=60% hexylamine, ○=30% hexylamine, ▽=15% hexylamine, △=30% hexylamine+10 ppb Pd.

given copper concentration the conversions increased significantly with the increased amount of hexylamine (15, 30, and 60 mol%), and the shapes of concentration–conversion curves were found to be parallel to each other (Figure 3). The positive effect of the amine on the conversion can be explained with larger amounts of copper acetylide monomers present in the reaction mixture and with the better solubilization of the formed copper acetylide species in nonpolar media. Both are crucial for either copper catalysis or feeding the very fast palladium cycle.

To distinguish between these two possible roles of copper complexes we examined the influence of the copper loading in the presence of added 10 ppb palladium and 30 mol% hexylamine. Results of these studies showed saturation-type dependence of the conversion on copper amount (Figure 3, top). The reaction rate increases precipitously with in-

creased copper loading in the range of 0–5 mol %, and becomes independent from 5 mol %. The presence of 10 ppb palladium complex ensures the work of active palladium cycles with extremely high turnover numbers. When the amount of copper is increased to 5 mol % (data points in the function of 0–5 mol % Cu, Figure 3), the exploitation of the palladium cycle is maximized, and further amounts of copper acetylide do not cause conversion enhancement. Similarly, in the reactions carried out without added palladium, the saturation point was reached at 0.25 mol % copper content supposedly due to the lower palladium level of the reaction mixture. On the basis of the observations, the similarity of these plot profiles (reactions without added palladium between 0–2.5 % copper content and 10 ppb palladium-catalyzed reactions in the range of 0–40 % copper content) suggests the significant role and catalytic activity of palladium contaminants in the components of the reaction.

In conclusion, we have demonstrated that the ppb levels of palladium impurities have a dramatic effect on the so-called copper-catalyzed Sonogashira reaction. The previous studies claim the existence of a copper-mediated catalytic cycle, but the significant sensitivity of the reaction to palladium contaminants questions this notion. However, the presence of copper in this coupling is undoubtedly very important, but on the basis of our results, we suppose that copper complexes play a role only in the formation of the copper acetylide species. Moreover, amines have multiple important roles in the coupling. They support the formation of the monomeric copper acetylide species from polymeric reservoirs by coordination, increase the solubility of the transition-metal complexes in organic media, and play important roles in the deprotonation of the acetylenes.

We suppose that the commercially available copper, carbonate, amine, and acetylene materials supply enough palladium for the "copper-catalyzed" Sonogashira coupling. Additionally, with the appropriate choice of reaction conditions, the power of the palladium could be fully exploited, and the developed reaction conditions offer an applicable, economic, and achievable synthesis of diaryl acetylenes using ppb amounts of palladium.

The demonstrated sensitivity of the reaction to palladium revealed mechanistic reconsiderations in connection not only with the Sonogashira coupling but, also, more traditional cross-coupling reactions performed under "palladium-free" conditions. We believe that when copper is present, the palladium is the engine of the Sonogashira coupling and the copper is just the fuel for its appropriate work by supplying the acetylide for transmetalation.

Finally, the prophecy of Plenio,[16] at least regarding the Sonogashira coupling: "*The Crownless Again Shall Be King*" has now been fulfilled.

Acknowledgements

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[17] We have found that Pd contamination of CuI, Cs_2CO_3, phenylacetylene, and the stirrer bar caused high conversions. For details see the Supporting Information.

[18] Concentration of reactants in our study was 3.75 times larger than was used in ref. [14c,f,h]. For concentration dependence, see the Supporting Information.

[19] The presence of 1–10 ppm palladium gave an identical reaction profile to literature data regarding copper catalyzed transformations (ref. [14f]). The positive effect of palladium was also observed in the presence of the [CuPhenPPh$_3$NO$_3$] complex. See the Supporting Information.

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[22] For data see the Supporting Information.

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[24] For data see the Supporting Information. For further studies we used hexylamine as the organic base for economic reasons.

[25] The positive effect of the amine also was observed in the presence of [CuPhenPPh$_3$NO$_3$] complex, see the Supporting Information.

[26] For data, see the Supporting Information.

[27] For the purity of copper see references [21] and [14a]; on the basis of ICP-MS analysis the copper complex contained ≈ 6 ng g^{-1} palladium; for the purity of carbonates see reference [9]; on the basis of ICP-MS analysis the K_2CO_3 contained 2.4 ng g^{-1} palladium. Calculating with the measured palladium content of the K_2CO_3, addition of 2.0 equiv base supplies 6 ppb (mol) Pd for the coupling.

[28] Supposing that the copper contains palladium ligated by PPh$_3$, with the addition of copper complex to the reaction mixture, the highly active palladium catalyst content also increases and its effect dominates when the amount of copper complex exceeds 2.5 mol%. Calculating with the measured palladium content of the copper complex (6 ng g^{-1} Pd content), addition of 2.5 mol% [Cu(PPh$_3$)$_2$NO$_3$] supplies 1 ppb (mol) Pd for the coupling.